PATENT APPLICATION

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Alangudi SANKARANARAYANAN

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For: COMPOSITION AND METHOD FOR USE OF PYRIDINIUM DERIVATIVES IN COSMETIC AND THERAPEUTIC APPLICATIONS

**SUBMISSION OF PRIORITY DOCUMENTS**

Commissioner for Patents
Washington, D.C. 20231

Sir:

Submitted herewith are certified copies of the priority documents on which a claim to priority was made under 35 U.S.C. § 119. The Examiner is respectfully requested to acknowledge receipt of said priority documents.

Respectfully submitted,

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Enclosures: India 828CAL99
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Date: January 10, 2003

# THE PATENTS ACT, 1970

It is hereby Certified that the annexed hereto is a true copy of the Complete Specification in respect of the Patent Application No. 828/Cal/99 filed on 06.10.99 by TORRENT PHARMACEUTICALS LTD., an Indian company of Central Plaza, 1st Floor, Room No.-106, 2/6, Sarat Bose Road, Calcutta-700 020, West Bengal, India and also at "TORRENT HOUSE", Near Dinesh Hall, Off. Ashram Road, Ahmedabad-380 009, Gujarat, India.

Witnesses in my hand

This the 20th day of June, 2001

This the 30th day of Jyaistha (1923) Saka

(K.K. Modak)
Asstt. Controller of Patents & Designs

The Patent Office
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FORM 2

THE PATENTS ACT, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

TITLE

# NOVEL COMPOUNDS FOR THE MANAGEMENT OF AGING-RELATED AND DIABETIC VASCULAR COMPLICATIONS, PROCESS FOR THEIR PREPARATION AND THERAPEUTIC USES THEREOF

APPLICANT

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AN INDIAN COMPANY.

The following specification particularly describes the nature of the invention and the manner in which it is to be performed.

# NOVEL COMPOUNDS FOR THE MANAGEMENT OF AGING-RELATED AND DIABETIC VASCULAR COMPLICATIONS, PROCESS FOR THEIR PREPARATION AND THERAPEUTIC USES THEREOF

## FIELD OF THE INVENTION

The present invention relates to a new class of compounds of pyridinium series and to their use in treatment of diabetes and related illnesses. More particularly the invention relates to compounds of this series, methods for their preparation, pharmaceutical composition containing these compounds and their use in the treatment of complications of diabetes mellitus. The compounds of this series exhibit AGE breaking activity, which is essential for the treatment of diabetic and aging-related complications including kidney disease, nerve damage, atherosclerosis, retinopathy and dermatological conditions. The invention also extends to the method of reversing the discoloration of teeth resulting from nonenzymatic browning in the oral cavity which comprises administration of an amount effective to reverse pre-formed advanced glycosylation crosslinks.

## BACKGROUND OF THE INVENTION

Maillard in 1912 found that reducing sugars, such as glucose and ribose react with proteins to form brown pigments. Further studies have shown that this

is an irreversible non-enzymatic reaction, which occurs in several natural systems including stored foodstuff. Maillard reaction occurs in two stages, early and advanced. Initially, proteins react with glucose to form stable Amadori products, which subsequently cross-links to form advanced glycation end products (AGE). In most cases, the formation of AGE also accompanies browning of the proteins and increase in the fluorescence.

In diabetes, where blood glucose level is significantly higher than normal, the reaction of glucose with several proteins such as haemoglobin, lens crystallin and collagen, gives rise to the formation of AGE, which in turn, is responsible for the complications associated with diabetes, such as nephropathy, microangiopathy, endothelial dysfunction and other organ dysfunctions. In addition, the activity of several growth factors, such as basic fibroblast growth factor, is also impaired. AGE products, unlike normal proteins in tissue, have a slower rate of turnover and replenishment. It has been reported that AGE products may in fact elicit a complex immunological reaction involving RAGE (Receptor for Advanced Glycation End Products) receptors and activation of several incompletely defined immunological processes. It has been documented that diabetes with evidence of microangiopathy and macroangiopathy also show evidence of oxidative stress, the mechanism of which has not been elucidated.

In vitro AGE formation can be studied in the laboratory by incubating reducing sugars, such as ribose or glucose with bovine serum albumin. AGE formation can be detected by increase in the fluorescence or increased cross reactivity with anti-AGE antibodies. The increase in fluorescence seems to precede formation of AGE specific antigenic epitopes. This increase in fluorescence is used to monitor the increased AGE formation in vitro (Brownlee M et al, Science 1986; 232:1629-1632). In addition to the increase in the fluorescence, one of the most important features of in vitro AGE formation is the formation of antigenic epitopes that are specific to AGE and not to the native proteins. Therefore, it is possible to raise antibodies against advanced glycation end products of one protein and use them to detect AGE formation in other proteins. This has served as an important analytical tool in AGE research.

Due to the clinical significance of AGE formation, many approaches are being used to diagnose, prevent, or revert AGE formation in the body. The formation of AGE could be inhibited by reacting with an early glycosylation product that results from the original reaction between the target protein and glucose. The inhibition was believed to take place as the reaction between the inhibitor and the early glycosylation product appeared to interrupt the subsequent reaction of the glycosylated protein with additional protein material to form the

cross linked late stage product. Compounds like aminoguanidine act to inhibit AGE formation by such mechanism.

The formation of AGE on long-lived proteins is also associated with cross-linking of these proteins. The AGE derived protein cross-links have been shown to be cleaved by compounds like N- phenacyl thiazolium bromide (PTB), which reacts with and cleaves covalent, AGE derived protein cross links (Vasan et al. Nature 1996; 382: 275-278 ; US 5,853,703, Date of Patent : Dec. 29, 1998). The mechanism of reducing the AGE content in tissues is expected to take place relatively rapidly, in contrast to aminoguanidine, which acts slowly by its very nature of mechanism of action. This current specification is related to compounds of pyridinium class, which break pre-formed AGE, like PTB, and in some cases even more effectively by than PTB.

## SUMMARY OF THE INVENTION

The main objective of the present invention is to provide a new class of compounds of the pyridinium series which are useful for the management of diabetes and aging related vascular complications and particularly in the treatment of complications of diabetes mellitus and other aging related conditions including kidney disease, nerve damage, atherosclerosis, retinopathy and dermatological conditions. The invention also extends the method to reverse the discoloration of

teeth resulting from nonenzymatic browning in the oral cavity which comprises administration of an amount effective to reverse the pre-formed advanced glycosylation crosslinks, etc.

Another object of the present invention is to provide compounds of the pyridinium series, which exhibit AGE breaking activities.

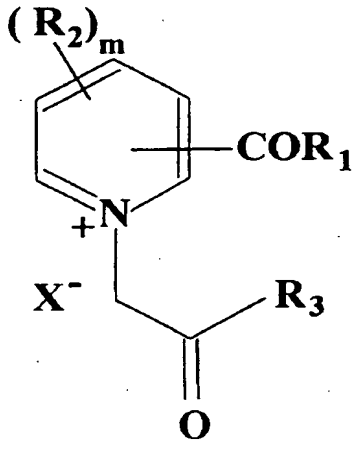
Yet another object of the present invention is to provide a method of preparation of compounds of the pyridinium series which exhibit AGE breaking activities.

Still another object of the invention is to provide pharmaceutical compositions with a new class of compounds of the pyridinium series according to the invention and their pharmaceutically acceptable salts in combination with suitable carriers, solvents, excepients, diluents and other media normally employed in preparing such compositions.

Still another object of the invention is to provide a method of treatment of a diabetic patient by administration of the compounds of the invention, either singly or in combination with drugs for anti-diabetic therapy, or pharmaceutically acceptable salts thereof in required dosage in admixture with pharmaceutically acceptable diluent, solvent, excepients, carriers or other media as may be appropriate for the purpose.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for a new class of AGE breakers, of general formula I,



(I)

wherein

$R_1$ is $-R_4-R_5$ or $-N(R_7)\,N\,(R_7)\,R_9$;

$R_4$ is selected from the group $-N(R_7)R_6O-$, $-N(R_7)R_6N(R_7)-$, $OR_6O$, $-OR_6N(R_7)-$, where $R_6$ is alkyl;

$R_5$ is selected from the group alkyl, aryl, including heteroaryl, $-COR_7$, $SO_2R_7$, $-C(S)\,NHR_7$, $-C(NH)NHR_7$, $-COR_{10}$,

$-C(O)NHR_7$ and $-N(R_7)\,N{=}C(R_7)(R_{10})$

where $R_7$ is selected from the group H, alkyl or aryl, including heteroaryl;

$R_2$ is selected from the group F, Cl, Br, I, $OR_7$, $NO_2$, alkyl, aryl including heteroaryl, formyl, acyl, $C(O)NR_7R_{10}$, $C(O)OR_7$, $NR_7R_{10}$, $N=C(R_7)(R_{10})$, $SR_7$, $SO_2NH_2$, $SO_2$ alkyl and $SO_2$aryl,

and m is 0, 1 or 2

$R_3$ is selected from the group $R_7$, $OR_7$, $N(R_7)(R_{10})$, $N=C(R_7)(R_{10})$, $N(R_7)N(R_7)(R_{10})$, $N(R_7)N=C(R_7)(R_{10})$ and $CH(R_7)C(O)R_8$

where $R_8$ is selected from the group $R_7$, $OR_7$ and $NR_7R_{10}$;

$R_9$ is selected from the group consisting of hydrogen, alkyl, aryl, including heteroaryl, $C(O)R_{10}$, $-SO_2R_{10}$, $-C(S)NHR_{10}$, $-C(NH)NH(R_{10})$, $-C(O)NHR_{10}$,

$R_{10}$ is selected for the group H, alkyl or aryl, including heteroaryl and in each case optionally different from substituent $R_7$

X is selected from group consisting of a halide ion, acetate ion, perchlorate ion, sulfonate ion, oxalate ion, citrate ion, tosylate ion, maleate ion, mesylate ion, carbonate ion, sulfite ion, phosphoric hydrogen ion, phosphonate ion, phosphate ion, $BF_4^-$, $PF_6^-$, etc.

with proviso that

(i) when two alkyl groups are present on the same carbon or nitrogen, they are optionally linked together to form a cyclic structure and

(ii) the nitrogen of heteroaryl ring of $R_{10}$, when present, is optionally quaternized with compound such as X-$CH_2C(O)$-$R_3$

As used herein, "alkyl" refers to an optionally substituted hydrocarbon group joined by single carbon-carbon bonds and having 1 to 8 carbon atoms joined together. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or unsaturated. The substituents are selected from F, Cl, Br, I, N, S, O and aryl. Preferably, no more than three substituents are present.

As used herein "aryl" refers to an optionally substituted aromatic group with atleast one ring having a conjugated pi- electron system, containing upto two conjugated or fused ring systems. Aryl includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The substituents are selected from F, Cl, Br, I, N, S, O and straight chain or branched $C_1$-$C_6$ hydrocarbon.

The novel compounds of the invention of general formula I having m as 0 and - $COR_1$ at position 3 are listed in Table 1A and the novel compounds of the invention of general formula I having m as 0 and - $COR_1$ at position 4 are listed in Table 1B. The following compounds suggested are by way of example alone of the representative compounds of the general formula I as defined above and in no way restrict the invention.

N,N'-Bis[3-carbonyl-1-(2-phenyl-2-oxoethyl)-pyridinium] hydrazine dibromide (compound 1):

N,N'-Bis[3-carbonyl-1-(2-ethoxy -2- oxoethyl)pyridinium]hydrazine dibromide (compound 2):

N,N'-Bis[3-carbonyl-1-(2-(2,4-dichlorophenyl)-2-oxoethyl)pyridinium]hydrazine dibromide (compound 3):

1- (2- Ethoxy -2- oxoethyl) -3- (2- (2- pyridyl) hydrazinocarbonyl) pyridinium bromide (compound 4):

1- (2- Thien -2'- yl -2- oxoethyl) -3- (methanesulfonyl hydrazinocarbonyl) pyridinium bromide (compound 5):

N,N'-Bis[3-carbonyl-1- (2- thien -2'- yl -2- oxoethyl)pyridinium]hydrazine dibromide (compound 6):

1- (2- Ethoxy -2- oxoethyl) -3- (2- (benzoyloxy) ethylaminocarbonyl) pyridinium bromide (compound 7):

1- (2- (2,4- Dichlorophenyl) -2- oxoethyl) -3- (2-(benzoyloxy)ethylamino-carbonyl) pyridinium bromide (compound 8):

1- (2- Thien -2'- yl -2- oxoethyl) -3- (2- (2- pyridyl) hydrazinocarbonyl) pyridinium bromide (compound 9):

1- (2- Phenyl -2- oxoethyl) -3- (2- (2- pyridyl)hydrazinocarbonyl) pyridinium bromide (compound 10):

1-(2-Phenyl-2-oxoethyl)-3-(hydrazinocarbonyl)pyridinium bromide (compound 11).

1-(2- Phenyl -2- oxoethyl) -3- (methanesulfonyl hydrazinocarbonyl) pyridinium bromide (compound 12):

1- (2- Ethoxy -2- oxoethyl) -3- (methanesulfonyl hydrazinocarbonyl) pyridinium bromide (compound 13):

1-(2-Phenyl-2-oxoethyl) -3- (phenylsulfonylhydrazino carbonyl) pyridinium bromide (compound 14):

1-(2-Phenyl-2-oxoethyl) -2-chloro-3- (phenylsulfonylhydrazino carbonyl) pyridinium bromide (compound 15):

1-(2- Phenyl -2- oxoethyl) -3- (2- (methoxy)carbonyl)ethyloxy carbonyl pyridinium bromide (compound 16):

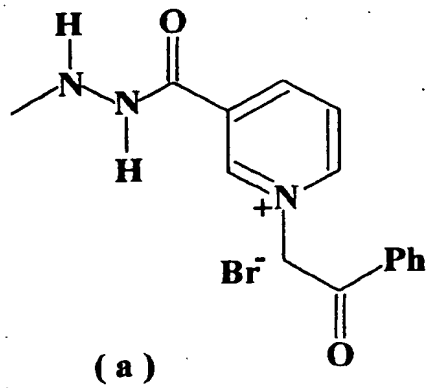
1-(2-Ethoxy -2- oxoethyl) -3- (2- (benzoyloxy) ethyloxy carbonyl) pyridinium bromide (compound 17):

1-(2- Thien -2'- yl -2- oxoethyl)-4-(2-(benzoyloxy)ethylaminocarbonyl) pyridinium bromide (compound 18):

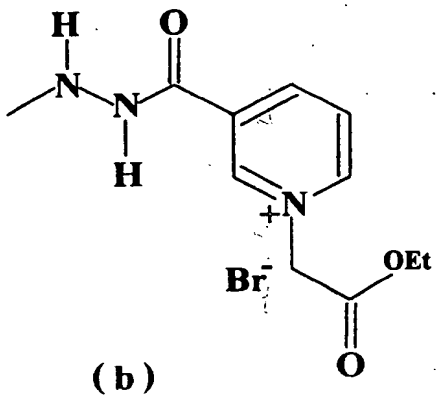
**Table 1A – Representative Pyridinium derivatives**

**(having m as 0 and -$COR_1$ at position 3)**

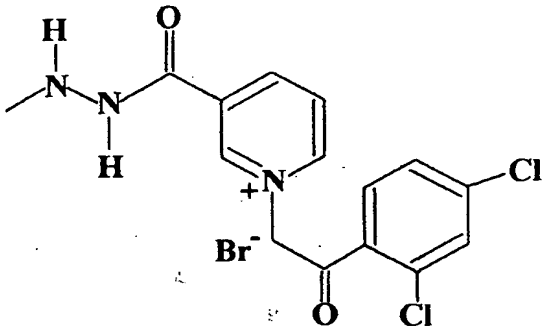
| Compound | -$R_1$ | -$R_2$ | -$R_3$ | -X |
|---|---|---|---|---|
| 1 | Structure(a) | - | phenyl | Br |
| 2 | Structure (b) | - | OEt | Br |
| 3 | Structure (c) | - | 2,4-dichlorophenyl | Br |
| 4 | NHNH-(2-pyridyl) | - | OEt | Br |
| 5 | $NHNHSO_2CH_3$ | - | 2-thienyl | Br |
| 6 | Structure (d) | - | 2-thienyl | Br |
| 7 | $NHCH_2CH_2OCOPh$ | - | OEt | Br |
| 8 | $NHCH_2CH_2OCOPh$ | - | 2,4-dichlorophenyl | Br |
| 9 | NHNH-(2-pyridyl) | - | 2-thienyl | Br |
| 10 | NHNH-(2-pyridyl) | - | phenyl | Br |
| 11 | $NHNH_2$ | - | phenyl | Br |
| 12 | $NHNHSO_2CH_3$ | - | phenyl | Br |
| 13 | $NHNHSO_2CH_3$ | - | OEt | Br |
| 14 | NHNH-$SO_2$phenyl | - | phenyl | Br |
| 15 | NHNH-$SO_2$phenyl | 2-Cl | phenyl | Br |
| 16 | $OCH_2CH_2OCOCH_3$ | - | phenyl | Br |
| 17 | $OCH_2CH_2OCOPh$ | - | OEt | Br |



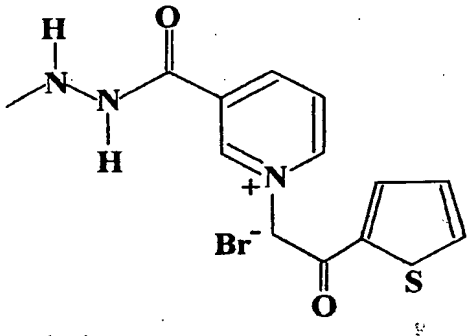
(a)



(b)



(c)



(d)

**Table 1B – Representative Pyridinium derivatives**

**(having m as 0 and -$COR_1$ at position 4)**

| Compound | -$R_1$ | -$R_2$ | -$R_3$ | -X |
|---|---|---|---|---|
| 18 | $NHCH_2CH_2OCOPh$ | - | 2-thienyl | Br |

According to the embodiment of the present invention, the present compounds are used for the treatment of diabetic complications, and aging related

complications including kidney disease, nerve damage, atherosclerosis, retinopathy, dermatological conditions and colouration of teeth occurring due to the higher levels of preformed AGE. The increased levels of preformed AGE can be brought under control by breaking the AGE products using compounds mentioned in the invention.

The invention also provides a process for the preparation of novel compounds of the pyridinium series.

The said process for the preparation of compound 1, comprises, adding a solution of phenacyl bromide in isopropanol to N,N'-bis-(nicotinyl)hydrazine dissolved in methanol, refluxing for six hours, cooling, filtering the precipitated solid, washing the solid with hot ethyl acetate and finally purifying the solid with 20 ml of methanol : ethyl acetate (3 : 1) to yield the desired compound.

Similarly, the other novel compounds of general formula I, are prepared from properly substituted pyridine derivatives followed by quarternization with appropriate reagent by refluxing in alcoholic solvents like, methanol, ethanol, propanol, etc and high boiling solvents like toluene or xylene etc, for 6 - 48 hrs. to give the desired compounds.

The in vitro AGE formation, studied in the laboratory, by incubating reducing sugar ribose, with protein bovine serum albumin, resulted in browning of

solution and increase in the fluorescence. Fluorescence was used as the criteria to monitor the increased AGE formation.

**Example 1**

**AGE breaker activity has been confirmed by the screening procedure as mentioned below:**

Materials:

Bovine serum albumin (fraction V) (BSA)

Ribose, analytical grade

Phosphate buffered saline (PBS)

Equipment:

Microplate ELISA Reader - Spectramax Plus (Molecular Devices, USA)

Microplate washer, (Bio -Tec Instruments, USA)

pH meter

Methods of experiment:

160 mg/ml of protein, bovine serum albumin, BSA and 1.6M glucose sugar were dissolved in phosphate buffered saline, PBS. Sodium azide was added at 0.02% concentration as a preservative. The solution was filtered asceptically through a 0.22 μM filter and kept for aging at 37°C for 16 weeks. After 16 weeks the solution was dialyzed against PBS, aliquoted and stored at - 20°C.

To determine the AGE breaking activity, 10μg/ml and 100μg/ml of the 16 weeks AGE-BSA was incubated with different concentrations of the test compounds at 37°C for 24 hours and AGE breaking activity of the test compounds by ELISA was determined.

ELISA was performed as follows:

1. Different concentrations of 16 weeks AGE-BSA were coated on a microtitre plate as standard. Each concentration is coated in triplicates.

2. The test samples were coated on microtitre plate at a concentration of 5 ng. to 20 ng per well in triplicates.

3. The plate was incubated at 37°C for one hour.

4. After incubation the plate was washed with PBST (PBS with 0.05% Tween 20).

5. Blocking with 5% skimmed milk in PBS at 37°C for one hour was done.

6. The plate was washed with PBST.

7. Primary antibody against AGE-BSA was added and the plate is incubated at 37°C for one hour.

8. The plate was washed with PBST

9. Secondary antibody anti rabbit HRPO (Horse-Radish Per Oxidase) conjugate was added and the plate is incubated at 37°C for one hour.

10. The plate was washed with PBST.

11. Colour development with OPD (orthophenylenediamine dihydrochloride) and hydrogen peroxide was done.

12. OD (optical density) at (450nm reading - 620nm reading) was measured after incubation at 37°C for 15 minutes with Microplate ELISA Reader.

The breaker activity of the compounds were determined by the following formula:

$$\% \text{ Breaker activity} = \frac{OD_{450\text{-}620}\text{Control} - OD_{450\text{-}620}\text{Test}}{OD_{450\text{-}620}\text{Control}} \times 100$$

$OD_{450\text{-}620}$Control= Absorbance of 20ng AGE-BSA after incubation at 37°C for 24 hours without test compound

$OD_{450\text{-}620}$Test= Absorbance of 20ng AGE-BSA after incubation at 37°C for 24 hours with required concentration of test compound

Using specific examples, the % AGE breaking activity was calculated and recorded in Table 2.

**Table 2**

| Sample | Concentration | % Breakage |
|---|---|---|
| PTB | 10 mM | 27 |
| | 20 mM | 47 |
| Compound 1 | 5 mM | 13 |
| Compound 4 | 10 mM | 30 |

| | | |
|---|---|---|
| Compound 6 | 5 mM | 53 |
| Compound 7 | 20 mM | 36 |
| Compound 16 | 10 mM | 16 |
| Compound 17 | 10 mM | 19 |

Hence compound 6 has significant AGE breaking activity i.e. a comparatively much superior potency vis - a - vis PTB.

The following examples give method of preparation of the specific novel compounds of the invention as given in Table 1. The following compounds suggested are by way of example alone and in no way restrict the invention.

**Example 2**

**Preparation of N,N'-bis [3-carbonyl-1- (2-phenyl-2-oxoethyl) pyridinium] hydrazine dibromide (compound 1):**

To a boiling solution of N,N'-bis-(nicotinyl)hydrazine (1.21 g., 0.005 mol.) in methanol (20 ml.), a solution of phenacyl bromide (1.99 g., 0.01 mol.) in isopropanol (10 ml.) was added and the reaction mixture was refluxed for 6 hrs. The reaction mixture was concentrated under vacuum (~10 ml.) and filtered. The obtained residue was washed with hot ethylacetate and then the isolated solid was powdered. It was recrystallised from a mixture of methanol and ethylacetate (3:1,

20 ml) to afford a pale yellow solid.

Yield : 60%

m.p. : 260 - 262°C (decomp.)

IR(KBr, $cm^{-1}$) : 1696 and 1680

$^1H$ NMR ($DMSOd_6$, 400MHz) δ: 11.65(2H,s), 9.56(2H,s), 9.21-9.16(4H,m), 8.49-8.45 (2H,m), 8.08-8.05 (4H,d), 7.81-7.77(2H,m), 7.68-7.64 (4H,m), 6.58 (4H,s)

Mass (m/z) : 479, 480

According to the above mentioned procedure the following compounds are synthesized by reacting the corresponding pyridine derivatives with appropriate reagents by refluxing in methanol, ethanol, propanol, toluene or xylene for 6 - 48 hrs. to get the desired compounds:

**Example 3**

**N,N'-Bis[3-carbonyl-1- (2- ethoxy -2-oxoethyl) pyridinium] hydrazine dibromide (compound 2):**

Yield : 47%

m.p. : 180 - 182°C (decomp.)

IR(KBr, $cm^{-1}$) : 1744, 1664

$^1H$ NMR ($DMSOd_6$, 400MHz) δ: 11.65 (2H,s), 9.62 (2H,s), 9.28-9.26 (2H,d), 9.17-9.15 (2H,d), 8.47-8.44 (2H,m), 5.77 (4H,s), 4.26 (4H,q), 1.27 (6H,t)

Mass (m/z) : 415, 416

**Example 4**

**N,N'-Bis[3-carbonyl-1- (2- (2,4- dichlorophenyl) -2- oxoethyl) pyridinium] hydrazine dibromide (compound 3):**

Yield : 24%

m.p. : 225 - 227°C (decomp.)

IR(KBr, $cm^{-1}$) : 1702, 1666

$^1H$ NMR ($DMSOd_6$, 400 MHz) δ: 11.69 (2H,s), 9.58 (2H,bs), 9.20-9.18 (4H,m), 8.49-8.47 (2H,m), 8.17-8.15 (2H,d), 7.92 (2H,bs), 7.78-7.76 (2H,d), 6.50 (4H,s)

Mass (m/z) : 615, 617, 618, 620.

**Example 5**

**1- (2- Ethoxy -2- oxoethyl) -3- (2- (2- pyridyl) hydrazinocarbonyl) pyridinium bromide (compound 4):**

Yield : 16%

m.p. : 210-212°C

IR (KBr, $cm^{-1}$) : 3140, 3005, 1732 and 1690

$^1H$ NMR ($DMSOd_6$, 400MHz) δ: 9.63 (1H,s), 9.27 (2H,d), 8.49-8.45 (1H,m) 8.13-8.07 (2H,m), 7.32-7.30 (1H,m), 7.12-7.11(1H,m), 5.77 (2H,s), 4.23 (2H,q), 1.25 (3H,t)

Mass (m/z) : 301, 302

**Example 6**

**1- (2- Thien -2'- yl -2- oxoethyl) -3- (methanesulfonyl hydrazinocarbonyl) pyridinium bromide (compound 5):**

Yield : 30 %

m.p : 199 – 200 °C

IR (KBr, $cm^{-1}$ ): 1714, 1673

$^1$HNMR ($DMSOd_6$, 400 MHz) δ: 11.38 (1H,s), 9.97 (1H,s) 9.51 (1H,s), 9.16 (1H,d), 9.06 – 9.04 (1H,m), 8.43 – 8.39 (1H,m), 8.25 – 8.21 (2H,m), 7.43 – 7.41 (1H,t), 6.45 (2H,s), 3.08 (3H,s).

Mass (m/z) : 340, 341, 342

**Example 7**

**N,N'-Bis[3-carbonyl-1- (2- thien -2'- yl -2- oxoethyl)pyridinium]hydrazine dibromide (compound 6):**

Yield : 33%

m.p. : 259 - 261°C (decomp.)

IR (KBr, $cm^{-1}$) : 3330, 1702, 1674, 1655 and 1626

$^1$H NMR ($DMSOd_6$, 400 MHz) δ: 11.59 (2H,s), 9.50 (2H,s), 9.15-9.08 (4H,m), 8.40-8.36 (2H,m), 8.17-8.14 (4H,m), 7.33(2H,t), 6.42 (4H,s)

Mass (m/z) : 491, 492.

**Example 8**

**1- (2- Ethoxy -2- oxoethyl) -3- (2- (benzoyloxy) ethylaminocarbonyl) pyridinium bromide (compound 7):**

Yield : 85%

m.p. : 132-134°C

IR (KBr, $cm^{-1}$) : 3210, 3067, 1726, 1687, 1656

$^1H$ NMR ($DMSOd_6$, 400 MHz) δ : 9.46 (1H,s), 9.37 (1H,t), 9.11(1H,t), 8.97 (1H,d), 8.33-8.29 (1H,m) 7.95-7.93 (2H,m), 7.63-7.59 (1H,m), 7.49-7.45 (2H,m), 5.65 (2H,s), 4.39 (2H,t), 4.19 (2H,q), 3.70-3.69 (2H,m), 1.20 (3H,t)

Mass (m/z) : 357, 358, 359

**Example 9**

**1- (2- (2,4- Dichlorophenyl) -2- oxoethyl) -3- (2-( benzoyloxy)ethyl aminocarbonyl) pyridinium bromide (compound 8):**

Yield : 75%

m.p. : 102-104°C

IR(KBr, $cm^{-1}$): 1703, 1685, 1675

$^1H$ NMR ($DMSOd_6$, 400 MHz) δ: 9.41-9.37 (2H,m), 9.03-8.98 (2H,m)8.34-8.30 (1H,m), 8.04 (1H,d), 7.91-7.89 (2H,m), 7.82 (1H,d),7.68-7.65 (1H,m), 7.58-7.55 (1H,m), 7.43 (2H,t), 6.35 (2H,s), 4.36 (2H,t), 3.68-3.64 (2H,m)

Mass (m/z) : 457, 458, 459, 460, 461, 462

**Example 10**

**1- (2- Thien -2'- yl -2- oxoethyl) -3- (2- (2- pyridyl) hydrazinocarbonyl) pyridinium bromide (compound 9):**

Yield : 10%

m.p. : 212-214°C (decomp)

IR(KBr, $cm^{-1}$) : 1685, 1649

$^1H$ NMR ($DMSOd_6$, 400 MHz) δ: 11.21 (1H,bs), 9.59 (1H,s), 9.19 (2H,d), 8.44 (1H,t), 8.27-8.24 (2H,m), 8.08 (1H,bs), 7.62 (1H,bs), 7.44 (1H,t), 6.85-6.79 (2H,m), 6.50 (2H,s)

Mass (m/z) : 339, 340, 341

**Example 11**

**1- (2- Phenyl -2- oxoethyl) -3- (2- (2- pyridyl) hydrazinocarbonyl) pyridinium bromide (compound 10):**

Yield : 4%

m.p. : 190°C (decomp)

IR(KBr, $cm^{-1}$) : 1683, 1670, 1648

$^1H$ NMR ($DMSOd_6$, 400 MHz) δ: 11.14 (1H,bs), 9.53 (1H,s), 9.18-9.13 (2H,m), 8.45-8.42 (1H,t), 8.08-8.06 (3H,m), 7.80 (1H,t), 7.67 (2H,t), 7.62-7.55 (1H,m), 6.83-6.76 (2H,m), 6.54 (2H,s)

Mass (m/z) : 333, 334, 335

**Example 12**

**1-(2-Phenyl-2-oxoethyl) -3- (hydrazinocarbonyl) pyridinium bromide (compound 11).**

Yield : 15%

m.p. : 215 – 216 °C

IR(KBr, $cm^{-1}$) : 1695, 1680

$^1$HNMR ($DMSOd_6$, 400 MHz) δ : 10.25 (1H,s) 9.65 (1H,s), 9.35 – 9.32 (2H,m), 8.90 – 8.88 (1H,m) 8.50 – 8.46 (2H,d), 8.21 – 8.17 (1H,m), 8.05 – 8.07 (2H,m), 6.50 (2H,s), 4.45 (2H,s).

Mass (m/z) : 256, 257.

**Example 13**

**1- (2- Phenyl -2- oxoethyl) -3- (methanesulfonyl hydrazinocarbonyl) pyridinium bromide (compound 12):**

Yield : 35%

m.p.: 227 – 228 °C

IR(KBr, $cm^{-1}$): 1710, 1702

$^1$HNMR ($DMSOd_6$, 400 MHz) δ : 11.30, (1H,s), 9.88 (1H,s), 9.41 (1H,s), 9.06 – 9.05 (1H,d) 8.98 – 8.96 (1H,d), 8.34 – 8.31 (1H,m), 7.97 (2H,d), 7.72 – 7.69 (1H,t), 7.59 – 7.56 (2H,t), 6.44 (2H,s), 2.99 (3H,s)

Mass (m/z): 334, 335

**Example 14**

**1-(2- Ethoxy -2- oxoethyl) -3- (methanesulfonyl hydrazinocarbonyl) pyridinium bromide (compound 13):**

Yield : 38%

m.p: 75- 76 °C

IR(KBr, $cm^{-1}$): 1739, 1697

$^1$HNMR ($DMSOd_6$, 400 MHz) δ : 11.39 (1H,s), 9.96 (1H,s), 9.56 (1H,s), 9.23 (1H,d), 9.06 (1H,d), 8.40 (1H,t), 5.75 (2H,s), 4.27 – 4.22 (2H,q), 3.08 (3H,s), 1.26 (3H,t)

Mass (m/z): 301, 302, 303

**Example 15**

**1-(2-Phenyl-2-oxoethyl)-3-(phenylsulfonylhydrazino carbonyl) pyridinium bromide (compound 14):**

Yield : 28%

m.p: 218 - 219°C

IR(KBr, $cm^{-1}$): 1687 , 1677

$^1$HNMR ($DMSOd_6$, 400 MHz) δ : 11.01 (1H,s), 9.53 (1H,s), 9.17 – 9.16 (2H,m), 8.44 (1H, t), 8.07 (2H,d), 7.80 (1H,t), 7.67 (2H,t), 7.18 (2H,t), 6.87 (2H,d), 6.77 (1H,t), 6.56 (2H,s).

Mass (m/z) : 461, 462

**Example 16**

**1- (2-Phenyl-2-oxoethyl)-2-chloro-3-(phenylhydrazino carbonyl) pyridinium bromide (compound 15):**

Yield : 23%

m.p. : 247 - 250°C (decomp)

IR(KBr, $cm^{-1}$): 1685 , 1679,

$^1$HNMR ($DMSOd_6$, 400 MHz) δ : 11.12 (1H,s), 9.49 (1H,s), 9.07 – 9.03(1H,m), 8.44 (1H, t), 8.07 (2H,d), 7.80 (1H,t), 7.67 (2H,t), 7.18 (2H,t), 6.87 (2H,d), 6.77 (1H,t), 6.50 (2H,s).

Mass (m/z) : 366, 367, 368

**Example 17**

**1-(2- Phenyl -2- oxoethyl) -3- (2- (methoxycarbonyl) ethyloxy carbonyl pyridinium bromide (compound 16):**

Yield : 40%

m.p. : 134-136°C

IR(KBr, $cm^{-1}$) :1710, 1670, 1668

$^1$HNMR ($DMSOd_6$, 400 MHz) δ :9.57(1H,s), 9.14-9.08(2H,m), 8.37-8.34(1H,m), 8.00-7.98(2H,d), 7.74-7.70(1H,t), 7.61-7.57(2H,t), 6.49(2H,s), 4.36-4.33(2H,t), 3.67-3.65(2H,t), 1.99(3H,s)

Mass (m/z) :328, 329, 330

**Example 18**

**1- (2- Ethoxy -2- oxoethyl) -3- (2- (benzoyloxy) ethyloxycarbonyl) pyridinium bromide (compound 17):**

Yield : 35%

m.p. : 142-143°C

IR(KBr, $cm^{-1}$) : 1728, 1685, 1660

$^1$HNMR ($DMSOd_6$, 400 MHz) δ : 9.60(1H,s), 9.20-9.18(1H,d), 7.04-9.02(1H,d), 8.33-8.29(1H,m), 7.90-7.88(2H,d), 7.58-7.57(1H,m), 7.46-7.42(2H,m), 5.67(2H,s), 4.71-4.68(2H,m), 4.58-4.56(2H,m), 4.15(2H,q), 1.16(3H,t)

Mass (m/z) : 358, 359, 360

**Example 19**

**1- (2- Thien -2'- yl -2- oxoethyl)-4-(2-(benzoyloxy)ethylaminocarbonyl) pyridinium bromide (compound 18):**

m.p. : 210 – 211°C

IR(KBr, $cm^{-1}$) : 1723, 1680, 1668

$^1$HNMR ($DMSOd_6$, 400 MHz) δ : 9.52 (1H,t), 9.14 (2H,d), 8.50 (2H,d), 8.25 – 8.21 (2H,m), 8.01 – 7.99 (2H,d), 7.67 (1H,t), 7.55 – 7.51 (2H,m), 7.42 – 7.40 (1H,m), 6.42 (1H,s) 4.47 – 4.45 (2H,t), 3.77 – 3.73 (2H, m).

Mass (m/z) : 395, 396

**Pharmaceutical Compositions**

Pharmaceutical compositions may be prepared with a pharmaceutically effective quantity of compounds of general formula I, individually or in combination. The following pharmaceutical formulations suggested are by way of example alone and in no way restrict the forms in which they can be used.

**Oral formulations**

Oral formulations may be administered as solid dosage forms for example pellets, powders, sachets or discreet units such as tablets or capsules and like. Other orally administered pharmaceutical preparations include monophasic and biphasic liquid dosage forms either in ready to use form or forms suitable for reconstitution such as mixtures, syrups, suspensions or emulsions. The preparations in addition may contain diluents, dispersing agents, buffers, stabilizers, solubilizers, surfactants, preservatives, chelating agents and/ or other pharmaceutical additives as are used. Aqueous or non aqueous vehicle or their combination may be used and if desired may contain suitable sweetener, flavoring agent or similar substances. In case of suspension or emulsion a suitable thickening agent or suspending agent or emulsifying agent may be present in addition. Alternatively, the compounds may be administered as such in their pure form unassociated with other additives for example as capsules or sachets. It may also be administered with a vehicle. Pharmaceutical preparations can have a slow,

delayed or controlled release of active ingredients as is provided by a matrix or diffusion controlled system.

When the present invention or its salts or suitable complexes is presented as a discreet unit dosage form like tablet, it may contain in addition medically inert excipients as are used in the art. Diluents such as starch, lactose, dicalcium phosphate, talc, magnesium stearate, polymeric substances like methyl cellulose, fatty acids and derivatives, sodium starch glycollate, etc. may also be used.

**Example 20**

**Preparation of oral dosage form:**

A typical tablet has the following composition:

| | |
|---|---|
| Active ingredient of formula I | as given above |
| Lactose | 135 mg |
| Starch | 76 mg |
| Polyvinyl pyrolidone (K-30) | 2 mg |
| Talc | 1.5 mg |
| Magnesium Stearate | 1.0 mg |

**Parenteral Formulations**

For parenteral administration, the compounds or their salts or suitable complexes thereof may be present in a sterile vehicle which may be an aqueous or non aqueous vehicle or a combination thereof. The examples of vehicles are

water, ethyl oleate, oils and derivatives of polyols, glycols and their derivatives. It may contain additives common in injectable preparations like stabilizers, solubilizers, pH modifiers, buffers, antioxidants, cosolvents, complexing agents, tonicity modifiers, etc.

Some suitable additives are for example tartrate, citrate or similar buffers, alcohol, sodium chloride, dextrose and high molecular weight polymers. Another alternative is sterile powder reconstitution. The compound may be administered in the form of injection for more than once daily administration, or intravenous infusion/ drip or suitable depot preparation.

**Example 21**

**Preparation suitable for parenteral administration has the following composition:**

| | |
|---|---|
| Active ingredient of formula I | as given above |
| Polyethylene glycol (400) | 0.75 ml |
| Sodium metabisulphite | 0.01% |
| Isotonic saline/ WFI | q.s. |

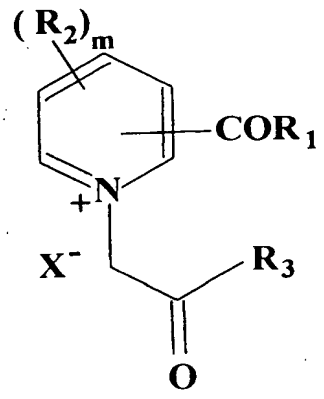
**Other Formulations**.

For the dermatological application and for the discoloration of teeth, the recommended formulations are lotions, oral rinse and toothpaste containing appropriate amount of the compounds of the general formula I.

The above examples are presented by way of illustration alone and in no way limit the scope of the invention.

WE CLAIM:

1. A compound of pyridinium series of general formula I, and its pharmaceutically acceptable salts, useful for the management of vascular complications associated with diabetes and aging related disorders,



(I)

wherein

$R_1$ is $-R_4-R_5$ or $-N(R_7)\,N\,(R_7)\,R_9$;

$R_4$ is selected from the group $-N(R_7)R_6O-$, $-N(R_7)R_6N(R_7)-$, $OR_6O$, $-OR_6N(R_7)-$,

where $R_6$ is alkyl;

$R_5$ is selected from the group alkyl, aryl, including heteroaryl, $-COR_7$, $SO_2R_7$, $-C(S)\,NHR_7$, $-C(NH)NHR_7$, $-COR_{10}$,

$-C(O)NHR_7$ and $-N(R_7)\,N=C(R_7)(R_{10})$

where $R_7$ is selected from the group H, alkyl or aryl, including heteroaryl;

$R_2$ is selected from the group F, Cl, Br, I, $OR_7$, $NO_2$, alkyl, aryl, including heteroaryl, formyl, acyl, $C(O)NR_7R_{10}$, $C(O)OR_7$,$NR_7R_{10}$, $N=C(R_7)(R_{10})$, $SR_7$, $SO_2NH_2$, $SO_2$ alkyl and $SO_2$aryl,

and m is 0, 1 or 2

$R_3$ is selected from the group $R_7$, $OR_7$, $N(R_7)(R_{10})$, $N=C(R_7)(R_{10})$, $N(R_7)N(R_7)(R_{10})$, $N(R_7)N=C(R_7)(R_{10})$ and $CH(R_7)C(O)R_8$

where $R_8$ is selected from the group $R_7$, $OR_7$ and $NR_7R_{10}$;

$R_9$ is selected from the group consisting of hydrogen, alkyl, aryl, including heteroaryl, $C(O)R_{10}$, $-SO_2R_{10}$, $-C(S)NHR_{10}$, $-C(NH)NH(R_{10})$, $-C(O)NHR_{10}$,

$R_{10}$ is selected for the group H, alkyl or aryl, including heteroaryl and in each case optionally different from substituent $R_7$

X is selected from group consisting of a halide ion, acetate ion, perchlorate ion, sulfonate ion, oxalate ion, citrate ion, tosylate ion, maleate ion, mesylate ion, carbonate ion, sulfite ion, phosphoric hydrogen ion, phosphonate ion, phosphate ion, $BF_4^-$, $PF_6^-$.

with proviso that,

(i) when two alkyl groups are present on the same carbon or nitrogen, they are optionally linked together to form a cyclic structure and

(ii) the nitrogen of heteroaryl ring of $R_{10}$, when present, is optionally quaternized with compound such as $X\text{-}CH_2C(O)\text{-}R_3$.

2. The compound as claimed in claim 1, wherein $-C(O)R_1$ group is at position 3 or 4.

3. The compound as claimed in claims 1 or 2, wherein the position for $-C(O)R_1$ group is at position 3.

4. The compound as claimed in claims 1, 2 or 3 wherein m is 0 or 1.

5. The compound as claimed in claims 1 or 4, wherein m is 0.

6. The compound as claimed in claims 1 or 2, wherein X is a halide ion.

7. The compound as claimed in claim 1, which is selected from the group consisting of the following compounds:

(a) N,N'-bis[3-carbonyl-1-(2-thien -2'- yl -2-oxoethyl) -3-pyridinium]hydrazine dibromide or a pharmaceutically acceptable salt thereof.

(b) 1-(2-ethoxy -2-oxoethyl) -3-(2-(2-pyridyl)hydrazinocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(c) 1-(2-ethoxy -2-oxoethyl) -3-(2-(benzoyloxy) ethylamino carbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(d)N,N'-bis[3-carbonyl-1-(2-phenyl-2-oxoethyl)pyridinium]hydrazine dibromide or a pharmaceutically acceptable salt thereof.

(e) 1-(2-phenyl-2-oxoethyl)-3-(hydrazinocarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

(f) 1-(2-thien -2'-yl -2-oxoethyl) -3-(methanesulfonyl hydrazinocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(g)N,N'-bis[3-carbonyl-1-(2-(2,4-dichlorophenyl)-2-oxoethyl)pyridinium] hydrazine dibromide or a pharmaceutically acceptable salt thereof.

(h) 1-(2-phenyl -2-oxoethyl) -3-(methanesulfonyl hydrazinocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(i) 1-(2-ethoxy -2-oxoethyl) -3-(methanesulfonyl hydrazinocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(j) 1-(2-phenyl-2-oxoethyl)-3-(phenylsulfonylhydrazino carbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(k) 1-(2-phenyl-2-oxoethyl)-2-chloro-3-(phenylsulfonyl hydrazino carbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(l) 1-(2-thien -2'-yl -2-oxoethyl)-4-(2-(benzoyloxy) ethyl aminocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(m)1- (2- (2, 4- dichlorophenyl) -2-oxoethyl) -3-(2- (benzoyloxy) ethylaminocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(n) 1-(2-phenyl -2-oxoethyl) -3-(2-(methoxy) carbonyl) ethyloxy carbonyl pyridinium bromide or a pharmaceutically acceptable salt thereof.

(o) 1-(2-ethoxy -2-oxoethyl) -3-(2-(benzoyloxy) ethyloxy carbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

8. A process for the preparation of compounds of the pyridinium series as claimed in claim 1, which comprises preparation of the properly substituted pyridine derivative, according to the desired end products, followed by quaternization of the substituted pyridine derivatives, with appropriate reagent by refluxing in alcoholic solvents and/or high boiling solvents for 6 - 48 hrs. to get the desired compounds.

9. The use of compound of general formula I as defined in claim 1, in the manufacture of a medicament for diabetic complications and aging-related diseases, including kidney disease, nerve damage, retinopathy, atherosclerosis, microangiopathy, endothelial dysfunctions, dermatological conditions, discoloration of teeth and other organ dysfunctions.

10. The use as claimed in claim 9, wherein said compound is selected from the group consisting of :

(a) N,N'-bis[3-carbonyl-1-(2-thien -2'-yl -2-oxoethyl) -3-pyridinium]hydrazine dibromide or a pharmaceutically acceptable salt thereof.

(b) 1-(2-ethoxy -2-oxoethyl) -3-(2-(2-pyridyl)hydrazinocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(c) 1-(2-ethoxy -2-oxoethyl) -3-(2-(benzoyloxy)ethylamino carbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(d) N,N'-bis[3-carbonyl-1-(2-phenyl-2-oxoethyl)pyridinium]hydrazine dibromide or a pharmaceutically acceptable salt thereof.

(e) 1-(2-phenyl-2-oxoethyl)-3-(hydrazinocarbonyl)pyridinium bromide or a pharmaceutically acceptable salt thereof.

(f) 1-(2-thien -2'-yl -2-oxoethyl) -3- (methanesulfonyl hydrazinocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(g)N,N'-bis [3-carbonyl -1- (2-(2,4-dichlorophenyl) -2-oxethyl) pyridinium] hydrazine dibromide or a pharmaceutically acceptable salt thereof.

(h) 1-(2-phenyl -2-oxoethyl) -3-(methanesulfonyl hydrazinocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(i) 1-(2-ethoxy -2-oxoethyl) -3-(methanesulfonyl hydrazinocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(j) 1-(2-phenyl-2-oxoethyl)-3-(phenylsulfonylhydrazino carbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(k) 1-(2-phenyl-2-oxoethyl)-2-chloro-3-(phenylsulfonyl hydrazino carbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(l) 1-(2-thien -2'-yl -2-oxoethyl)-4-(2-(benzoyloxy) ethylaminocarbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(m) 1-(2-(2,4-dichlorophenyl) -2-oxoethyl) -3-(2-(benzoyloxy)ethylamino carbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

(n) 1-(2-phenyl -2-oxoethyl) -3-(2-(methoxy) carbonyl) ethyloxy carbonyl pyridinium bromide or a pharmaceutically acceptable salt thereof.

(o) 1-(2-ethoxy -2-oxoethyl) -3-(2-(benzoyloxy) ethyloxy carbonyl) pyridinium bromide or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition for treatment of diabetic complications and aging related diseases which comprises a pharmaceutically effective amount of one or more compounds of general formula I, as defined in claim 1, or pharmaceutically acceptable salt(s) thereof in admixture with a pharmaceutically acceptable carrier, diluent, solvent or excepient.

12. A pharmaceutical composition as claimed in claim 11, in the form of an oral formulation.

13. A pharmaceutical composition as claimed in claim 12, wherein said pharmaceutically acceptable carrier is selected from one or more of the compounds starch, lactose, polyvinyl pyrolidone (K-30), talc and magnesium stearate.

14. A pharmaceutical composition as claimed in claim 11, in the form of a parenteral formulation.

15. A method for the preparation of a parenteral formulation as claimed in claim 14, wherein the said process comprises dissolving the active ingredient of general formula I, as defined in claim 1, in polyethylene glycol 400 and diluting the solution so obtained, with an isotonic solution or water to the desired concentration.

16. Pharmaceutical composition as claimed in claim 11, in the form of lotions, oral rinse and toothpaste.

17. A method for treating a diabetic patient by breaking the preformed AGE, within said patient, which comprises, administering an effective amount of a compound as claimed in claim 1, either singly, or in combination with other drugs for antidiabetic therapy.

18. A method of preventing or treating diseases caused by diabetes and aging related complications, which comprises, administering to a patient in need thereof, an effective amount of a compound of formula I, as claimed in claim 1, either singly or in combination with a pharmaceutically acceptable carrier, diluent or excepient .

19. The method as claimed in claim 18, wherein the disease prevented or treated is a nephrological disorder, neurological disorder, atherosclerosis, retinal

disorder, dermatological disorder, non-enzymatic browning of oral cavity, endothelial or other organ dysfunction and growth impairment.

20. A method of making a pharmaceutical composition, substantially as herein described, particularly with reference to the examples.

21. A process for the preparation of compounds of the pyridinium series, substantially as herein described, particularly with reference to the examples.

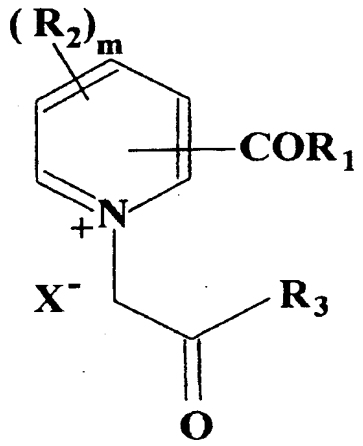
Dated this 6th day of October, 1999.

(S.D. AHUJA)
of D. P. AHUJA & CO.
APPLICANTS' AGENT

"NOVEL COMPOUNDS FOR THE MANAGEMENT OF AGING-RELATED AND DIABETIC VASCULAR COMPLICATIONS, PROCESS FOR THEIR PREPARATION AND THERAPEUTIC USES THEREOF"

## ABSTRACT

The invention discloses novel compounds of the pyridinium series useful for the management of diabetes and aging-related vascular complications, including kidney disease, nerve damage, atherosclerosis, retinopathy, dermatological disorders and discoloration of teeth, by breaking preformed AGE, of the general formula I, or pharmaceutically acceptable salts thereof,



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wherein, $R_1$, $R_2$, $R_3$, X and m are as defined in the specification.

The invention also discloses, method for preparation of the novel compounds of the series and pharmaceutical composition having one or more compounds as defined above as active ingredients.

The invention further discloses a method of treatment of a diabetic patient by administering the compounds as defined above, either singly or in combination with drugs for antidiabetic therapy.